

### Remarks

Claims 1 to 17 were pending. By this Amendment, claims 4 and 6 were cancelled and claims 1, 2, 3, 5, 11, 12, 13, and 17 were amended. Applicants maintain that no new matter has been added by these amendments and therefore respectfully request that the Examiner enter the amendments presented. Amended claims 1 to 3, 5, and 7 to 17 are now pending in this application.

The Examiner rejected claims 1 to 5, 7, 9, 10, 13, and 17 under 35 U.S.C. § 103(a) as allegedly obvious over the combined teachings of Schromm *et al.* I (U.S. Patent No. 4,460,581) and Schromm *et al.* II (U.S. Patent No. 5,223,614).

In response, applicants again respectfully traverse the Examiner's obviousness rejection and contend that the rejection is improper. A *prima facie* case of obviousness requires the satisfaction of three criteria: (i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (ii) there must be a reasonable expectation of success; and (iii) the references when combined must teach or suggest all of the claim limitations. *See* M.P.E.P. § 2143.

In support of the rejection, the Examiner cites *In re Payne*, 203 U.S.P.Q. 245 (C.C.P.A. 1979) and *Ex parte Wiseman*, 98 U.S.P.Q. 277 (Pat. Off. Board App. 1953), both of which involve facts are distinct from those presented in the instant situation. For example, *In re Payne* affirmed an obviousness rejection where the "claimed compounds differ from the primary reference compounds only in the sulfur-carbamoyloximino moiety linkage", while the "secondary references were cited for their disclosure that phosphonated dithiacycloalkanes exhibit pesticidal activity when substituted at any ring position." *Id.* at 248. In contrast, the instant Examiner has cited no reference in support of the hydroxy to methoxy substitution that the Examiner's rejection requires, so the holding in *In re Payne* is different from the instant rejection, which is accordingly deficient. Similarly, *Ex parte Wiseman* affirmed an obviousness rejection of a fluoro compound over a chloro analogue. However, the Examiner in *Ex parte Wiseman* relied on the Mochel reference for the teaching of the fluoro analogue of the compound disclosed in the Carothers *et al.* reference (the primary reference). The Examiner has no such reference in the instant rejection, so the rejection in *Ex parte Wiseman* is different

from the instant rejection as the Examiner here has cited no reference in support of the hydroxy to methoxy substitution that the Examiner's rejection requires.

Applicants are unsure why the Examiner cited *In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985), in support of the rejection since *In re Grabiak* reversed the Examiner's obviousness rejection of a thioester compound over its analogous ester compound because "The PTO cited no pertinent reference showing or suggesting to one of ordinary skill in the art the change of a thioester for an ester group. In the absence of such a reference, there is inadequate support for the PTO's position that this modification would *prima facie* have been obvious." *Id.* at 872 (emphasis added). Similarly, the lack of any suggestion in the prior art cited by the Examiner to substitute methoxy for hydroxy renders the Examiner's rejection improper. See, e.g., *Ex parte Brouard*, 201 U.S.P.Q. 538, 540 (Bd. Pat. App. 1976).

Conclusory statements do not adequately address the issue of motivation to combine. *In re Lee*, 61 U.S.P.Q. 1430, 1435 (Fed. Cir. 2002). The factual question of motivation is material to patentability, and cannot be resolved on subjective belief and unknown authority. *In re Lee*, 61 U.S.P.Q. 1430, 1434 (Fed. Cir. 2002). Thus, not only must the requisite findings be made, based on evidence of record, but the reasoning by which the findings are deemed to support the agency's conclusion must be explained. *Id.* The Examiner is apparently attempting to evade the requirement to substantiate the hydroxy to methoxy substitution necessary for the Examiner's rejection. Applicants respectfully request such substantiation for the Examiner's reliance. See M.P.E.P. § 2144.03.

Accordingly, far from "merely contending that the rejection is improper" as the Examiner alleges (Final Office Action, page 4), applicants have explained in detail why *In re Payne* and *Ex parte Wiseman* do not support the Examiner's rejection and why *In re Grabiak* and *Ex parte Brouard* involve similar situations and show why the Examiner has not established a *prima facie* case of obviousness. Since a *prima facie* case of obviousness has not been established, there is no need for comparative tests or a showing of "unexpected results", since there is no rejection that must be overcome. *In re Benno*, 226 U.S.P.Q. 683 (Fed. Cir. 1985). Therefore, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner also rejected claims 13 and 17 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

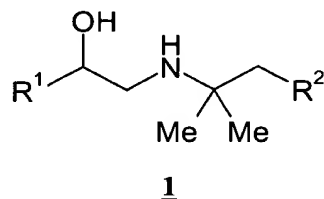
In response, applicants have amended claims 13 and 17 as suggested by the Examiner. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Applicants respectfully submit that all the pending claims are allowable and therefore solicit a Notice of Allowance for all of the pending claims. If the Examiner feels that a telephone interview would be helpful in advancing prosecution of this application, the Examiner is invited to contact the attorney below.

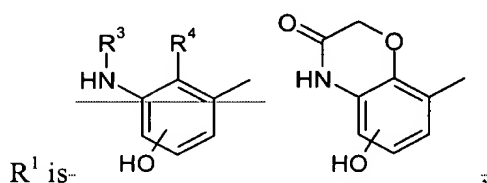
**Version of the Specification with Markings to Show Changes Made by this Amendment**

In accordance with 37 C.F.R. § 1.121(c)(1)(ii), the following marked up version of the specification amended herein is provided to show all of the changes relative to the previous version before the amendments herein.

--1. (Twice amended) A compound of formula 1



wherein:

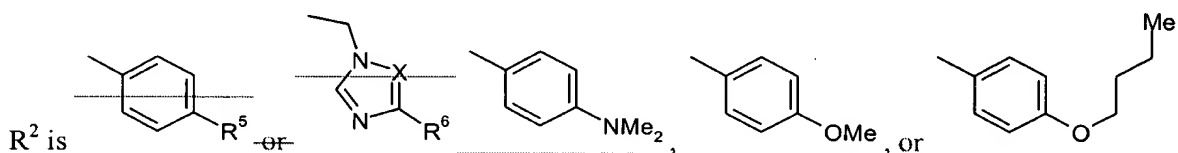


wherein:

~~R<sup>3</sup> is a benzyl group optionally substituted by a methoxy group;~~

~~R<sup>4</sup> is a hydrogen atom; or~~

~~R<sup>3</sup> and R<sup>4</sup> together are a -CO-CH<sub>2</sub>-O- bridge, the carbonyl group of the bridge being bound to the nitrogen; and~~



wherein:

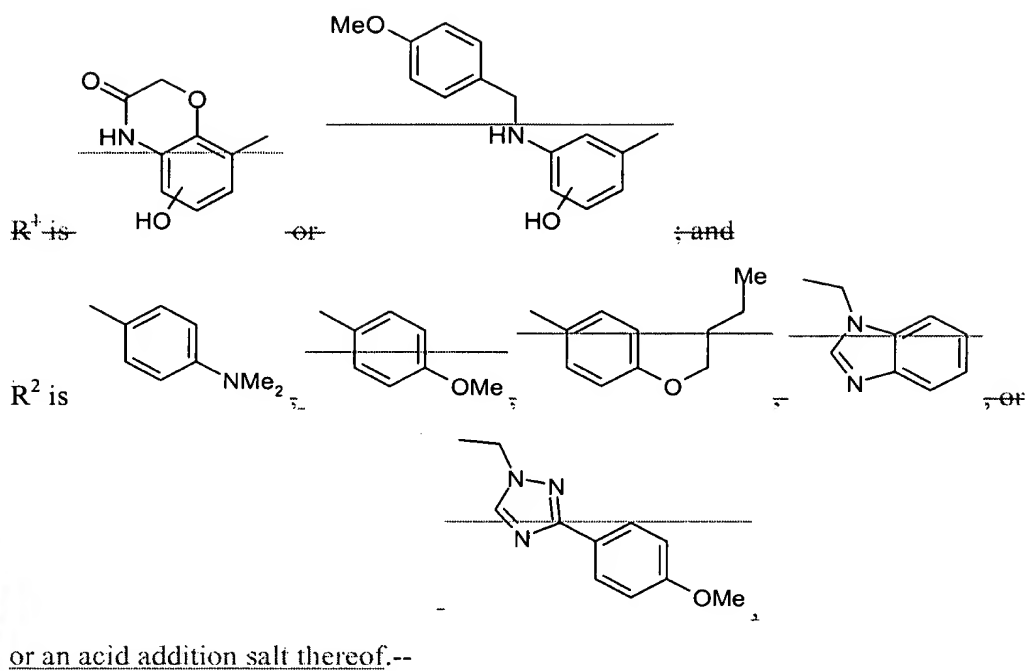
~~R<sup>5</sup> is a dimethylamino, methoxy, or butoxy group;~~

~~X is a nitrogen or a carbon atom; and~~

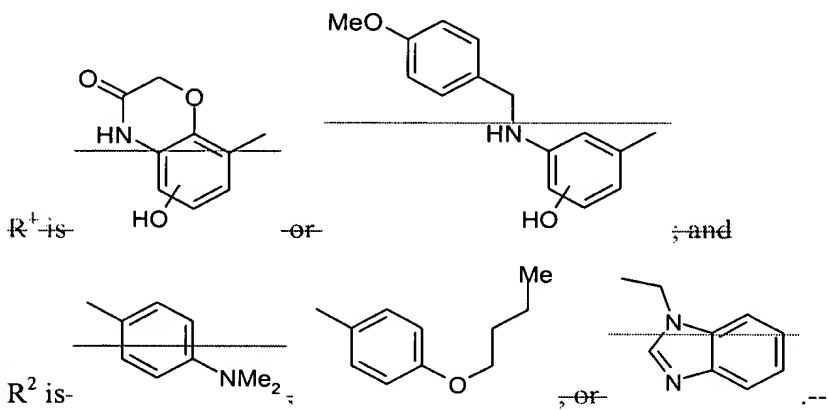
~~R<sup>6</sup> is a methoxyphenyl group, if X is nitrogen, or is an anellated phenyl ring also linked to X, if X is carbon;~~

or an acid addition salt thereof.--

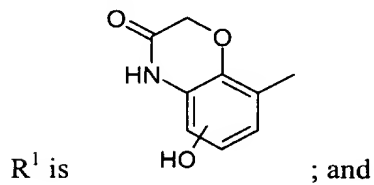
--2. (Twice amended) The compound of formula 1 according to claim 1, wherein:



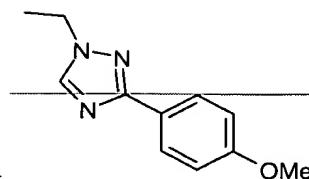
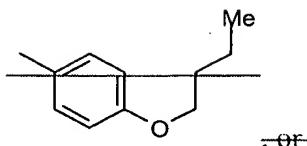
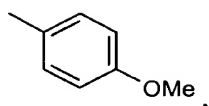
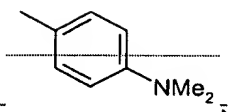
--3. (Twice amended) The compound of formula **1** according to claim 1, wherein:



--5. (Twice amended) The compound of formula **1** according to claim 1, wherein:



R<sup>2</sup> is-



or an acid addition salt thereof.--

--11. (Twice amended) The compound according to one of claims 1, 2, ~~to 3~~, 5, ~~6 or 8~~, ~~to 9~~, or 10, wherein the acid addition salt thereof is formed with a pharmacologically acceptable acid.--

--12. (Twice amended) A method of treating bronchial asthma, the inflammatory component in COPD, premature onset of labor in midwifery (tocolysis), atrio-ventricular block, bradycardiac hearth rhythm disorders, circulatory shock, or itching and inflammation of the skin in a host in need of such treatment, the method comprising administering to the host the compound according to one of claims 1, 2, 3, 5, ~~to 6 or 8~~, 9, ~~to 10~~ or 10.--

--13. (Twice amended) A pharmaceutical ~~preparation~~composition comprising a compound according to one of claims 1, 2, 3, 5, ~~to 6 or 8~~, 9, ~~to 10~~ or 10 and a conventional excipient or carrier.--

--17. (Amended) A pharmaceutical ~~preparation~~composition comprising a compound according claim 7 and a conventional excipient or carrier.--

**Certificate of Mailing Under 37 C.F.R. § 1.8(a)**  
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on June 24, 2003.

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6-24-2003

Dated

Respectfully submitted,

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